# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>14 March 2001 (14.03.01) | |
| **International application No.**<br>PCT/EP00/06870 | **Applicant's or agent's file reference**<br>H153030HW4FD |
| **International filing date** (day/month/year)<br>18 July 2000 (18.07.00) | **Priority date** (day/month/year)<br>21 July 1999 (21.07.99) |
| **Applicant**<br>KAVERI, Srinivas et al | |

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

31 January 2001 (31.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|---|
| **The International Bureau of WIPO**<br>**34, chemin des Colombettes**<br>**1211 Geneva 20, Switzerland** | Authorized officer<br>Pascal Piriou |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

Form PCT/IB/331 (July 1992)

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PORTAL, Gérard
CABINET BEAU DE LOMENIE
158, Rue de l'Université
75340 PARIS CEDEX 07
FRANCE

15 NOV. 2001

# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 12.11.2001 |
| Applicant's or agent's file reference: H153030-4WO | **IMPORTANT NOTIFICATION** |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/EP00/06870 | 18/07/2000 | 21/07/1999 |

Applicant: INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE M

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

| Name and mailing address of the IPEA/ | Authorized officer |
|---|---|
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Danti, B<br><br>Tel.+49 89 2399-8161 |

Form PCT/IPEA/416 (July 1992)

TENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | **FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
|---|---|---|
| H153030HW4FD | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/EP 00/06870 | 18/07/2000 | 21/07/1999 |
| Applicant | | |
| INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE M | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No
EP 00/06870

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 7 G01N33/68 C07K7/06 A61K38/08 A61K39/395

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | C. A. FULCHER ET AL.: "Localization of human factor FVIII inhibitor epitopes to two polypeptide fragments." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 82, November 1985 (1985-11), pages 7728-7732, XP002125713 NATIONAL ACADEMY OF SCIENCE. WASHINGTON., US ISSN: 0027-8424 the whole document | 1-27 |
| A | WO 94 11013 A (DUKE UNIVERSITY) 26 May 1994 (1994-05-26) claims | 1-27 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 29 November 2000 | 07/12/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Griffith, G |

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | J. G. G. GILLES ET AL.: "Anti-factor VIII antibodies of hemophiliac patients are frequently directed towards nonfunctional determinants and do not exhibit isotypic restriction." BLOOD, vol. 82, no. 8, 15 October 1993 (1993-10-15), pages 2452-2461, XP002096815 PHILADELPHIA, PA, US ISSN: 0006-4971 the whole document --- | 1-27 |
| A | K. FIJNVANDRAAT ET AL.: "A human alloantibody interferes with binding of factor IXa to the factor VIII light chain." BLOOD, vol. 91, no. 7, 1 April 1998 (1998-04-01), pages 2347-2352, XP002118155 PHILADELPHIA, PA, US ISSN: 0006-4971 the whole document --- | 1-27 |
| A | S. EHRENFORTH ET AL.: "Incidence of development of factor VIII and factor IX inhibitors in heamophiliacs." LANCET THE., vol. 339, 7 March 1992 (1992-03-07), pages 594-598, XP002125714 LANCET LIMITED. LONDON., GB ISSN: 0140-6736 cited in the application --- | |
| A | E. L. SAENKO ET AL.: "A role for the C2 domain of factor VIII in binding to von Willebrand factor." JOURNAL OF BIOLOGICAL CHEMISTRY., vol. 269, no. 15, 15 April 1994 (1994-04-15), pages 11601-11605, XP002125715 AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD., US ISSN: 0021-9258 cited in the application --- | |

-/--

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | E. L. SAENKO ET AL.: "Slowed release of thrombin-cleaved factor VIII from von Willebrand factor by a monoclonal and a human antibody is a novel mechanism for factor VIII inhibition." JOURNAL OF BIOLOGICAL CHEMISTRY., vol. 271, no. 44, 1 November 1996 (1996-11-01), pages 27424-27431, XP002125716 AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD., US ISSN: 0021-9258 cited in the application | |

1

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
EP 00/06870

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9411013 A | 26-05-1994 | AU 5602394 A | 08-06-1994 |
| | | US 5587310 A | 24-12-1996 |

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number
WO 01/07918 A1

(51) International Patent Classification[7]: G01N 33/68, C07K 7/06, A61K 38/08, 39/395

(21) International Application Number: PCT/EP00/06870

(22) International Filing Date: 18 July 2000 (18.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99401841.4 21 July 1999 (21.07.1999) EP

(71) Applicants *(for all designated States except US)*: **INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)** [FR/FR]; 101 Rue de Tolbiac, F-75654 Paris Cedex 13 (FR). **BAYER PHARMA** [FR/FR]; 13 rue Jean Jaurès, F-92807 Puteaux (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KAVERI, Srinivas** [FR/FR]; 15 rue Lucien et Edouard Gerber, F-92240 Malakoff (FR). **LACROIX-DESMAZES, Sébastien** [FR/FR]; 33 rue de St.Cloud, F-92410 Ville d'Avray (FR). **KAZATCHKINE, Michel** [FR/FR]; 1 rue Le Goff, F-75005 Paris (FR).

(74) Agents: PORTAL, Gérard et al.: Cabinet Beau de Loménie, 158 rue de l'Université, F-75340 Paris Cedex 07 (FR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 01/07918 A1

(54) Title: CATALYTIC ANTI-FACTOR VIII ALLO-ANTIBODIES

(57) Abstract: The present invention relates to a method of determining the presence of catalytic anti-Factor VIII allo-antibodies capable of degrading Factor VIII in a mammal, and of characterising the cleavage sites in said Factor VIII molecule by said catalytic anti-Factor VIII allo-antibodies. It also relates to an anti-Factor VIII allo-antibody-catalysed Factor VIII degradation inhibitor; and to a pharmaceutical composition comprising said catalytic anti-Factor VIII allo-antibodies which are capable of degrading Factor VIII and which originate from said method of determination; and further to a pharmaceutical composition comprising said anti-Factor VIII allo-antibody-catalysed Factor VIII degradation inhibitor. Finally, the present invention relates to the application in therapeutics of said anti-Factor VIII allo-antibody-catalysed Factor VIII degradation inhibitor, of a pharmaceutical composition comprising said catalytic anti-Factor VIII allo-antibodies which are capable of degrading Factor VIII and which originate from said method of determination, and of a pharmaceutical composition comprising said anti-Factor VIII allo-antibody-catalysed Factor VIII degradation inhibitor.

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| H153030-4WO | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/EP00/06870 | 18/07/2000 | 21/07/1999 |

International Patent Classification (IPC) or national classification and IPC
G01N33/68

15 NOV 2001

Applicant
INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE M ...umenie

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 31/01/2001 | 12.11.2001 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Weijland, A<br>Telephone No. +49 89 2399 7490 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06870

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

1-21 as originally filed

**Claims, No.:**

1-27 as originally filed

**Drawings, sheets:**

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-16,20-27 |
| | No: | Claims | 17-19 |
| Inventive step (IS) | Yes: | Claims | 1-16, 20-27 |
| | No: | Claims | 17-19 |
| Industrial applicability (IA) | Yes: | Claims | 1-27 |
| | No: | Claims | |

2. Citations and explanations
   **see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
**see separate sheet**

The following documents (D) are referred to in this report:

D1: C. A. FULCHER ET AL.: 'Localization of human factor FVIII inhibitor epitopes to two polypeptide fragments.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 82, November 1985 (1985-11), pages 7728-7732, XP002125713 NATIONAL ACADEMY OF SCIENCE. WASHINGTON., US ISSN: 0027-8424

**SECTION V**

1. Novelty (Article 33(2) PCT)

1.1 The subject matter of claims 1-16 and 20-27 is novel.

Claim 1, relating to determining the presence of anti-Factor VIII allo-antibodies capable of **degrading** Factor VIII comprising the detection of degradation of Factor VIII by anti-Factor VIII allo antibodies, is not disclosed in the prior art documents.

Claims 13-16 and 20-22, relating to sequences (claims 13-15), peptides (claim 16) or inhibitors (claims 20-22) having defined sequences according to claims 13-15 are not disclosed in the prior art documents.

Claims 23-27, relating to pharmaceutical compositions including anti-Factor VIII allo-antibodies or its inhibitors (claims 23 and 26 respectively) and uses of anti-Factor VIII allo-antibodies for the preparation of a pharmaceutical composition (claims 24, 25) and inhibitors thereof (claim 27), are not disclosed in the prior art documents.

1.2 The subject matter of claims 17 to 19 is not novel.

Claim 17 is related to a degradation inhibitor. Compounds that encompass the scope of this claim are mentioned on page 6 (lines 20 to 30) of the description, such as PMSF or AEBSF that are commercially available and inhibit the cleavage of Factor VIII at certain positions. The existence of these molecules anticipates

the subject matter of claims 17-19, **since a hitherto unknown property,** i.e. inhibiton of Factor VIII cleavage by allo-antibodies, **cannot render a known product,** i.e. AEBSF, **novel** (the Guidelines C-III 4.8).

2. Inventive Step (Article 33(3) PCT)

2.1 The subject matter of claims 1-12 would appear to involve an inventive step.

D1 is considered to be the closest prior art. D1 (abstract; page 7729, left column, 8 paragraph) describes the localization of human factor VIII inhibitor epitopes for 22 allo-antibodies by immunoblotting. Claim 1 differs from D1 in that it relates to a method of defermining the presence of anti-Factor VIII allo-antibodies by determining the **degradation** of Factor VIII.

The skilled person, equipped with knowledge of D1, would never be motivated to arrive at the subject matter of claim 1, since it has not been suggested in D1 alone or in combination with any other prior art document that said allo-antibodies **degrade** Factor VIII. The same applies to claims 2-12.

2.2 The subject matter of claims 13-16, 20-22 would appear to involve an inventive step.

Claim 13-16 and 20-22, relating to specific peptides sequences that are novel (see section 2.1), would appear to involve an inventive step, since it has not been suggested in the prior art documents that these sequences as part of peptides (claims 13-16) or inhibitors (claims 20-22) are capable of inhibiting the **degradation** of Factor VIII.

2.3 The subject matter of claims 23-27 would appear to involve an inventive step.

D1 (abstract; page 7732, right column) suggests the use of peptides derived from epitopes on Factor VIII and recognized by allo-antibodies as therapeutic agents to block inhibition of Factor VIII activity.

Claims 23 and 24 differ from D1 in that they relate to a pharmaceutical

composition comprising an anti-Factor VIII allo-antibody (claim 23) or the use thereof in the preparation of a pharmaceutical composition.

Claims 23 and 24 would appear to involve an inventive step, since the presence of degrading anti-Factor VIII allo-antibodies as part of a pharmaceutical composition or the use thereof has not been suggested before in the art and implicates a functional role of said antibodies by inhibiting pro-coagulant activity faster than non-catalysing anti-Factor VIII antibodies (page 13, lines 13-15 of the description). For the same reasons mentioned above, also claim 25 involves an inventive step.

Claims 26 and 27, relating to a pharmaceutical composition containing a Factor VIII degradation inhibitor or the use thereof in the preparation of a composition would appear to involve an inventive step, since the degradation of Factor VIII by an allo antibody has not been suggested in the art and consequently neither the use of its inhibitors.

**SECTION VII**

3. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 is not mentioned in the description, nor is this document identified therein.

**SECTION VIII**

4. The use of "preferably" renders the passage "preferably activated with cyanogen bromide" in claim 4 non-limiting for the scope of said claim and introduces ambiguity in the protection sought and therefore contravenes Article 6 PCT.

5. In order to meet the requirements of clarity the term "sequence" in claims 13-15 needs to be replaced by "peptide sequence" Article 6 PCT.

6. The term "peptide or non-peptide analogue" in present claim 16 introduces ambiguity in the scope for which protection is sought and therefore contravenes Article 6 PCT.

7. The passage "characterized in that it is capable of inhibiting any site in the Factor VIII molecule which is susceptible to being lysed by an anti-Factor VIII allo-antibody" is defined as results to be achieved and therefore lacks clarity (Article 6 PCT). It appears possible to define the subject matter in more concrete terms, viz. in terms how the effect, i.e. inhibiting any site in the Factor VIII molecule which is susceptible to being lysed, is to be achieved (see e.g. the technical features of claims 13-15).

8. The subject matter of claim 17 does not meet the requirements of Article 6 PCT in that the subject matter for which protection is sought is not defined. Said claim attempts to define the subject-matter in terms of the result to be achieved and is not allowable, because it appears possible to define the subject matter in more concrete terms, viz. in terms of how the effect, i.e. the inhibition of the activity of a Factor VIII allo-antibody, is to be achieved (see e.g. the technical features in claims 18 and 19).

9. Claims 24 and 27 suffer from a lack of clarity (Article 6 PCT), because they are formulated as second medical indication claims, but are not defined by a medical indication. The passage "treatment of a mammal.... in the blood thereof" in claims 24 and 27 defines no medical indication (i.e. disease).

10. The use of "in particular" renders the passage "in particular for the treatment of a mammal suffering...." in claim 27 non-limiting for the scope of said claim and introduces ambiguity in the protection sought and therefore contravenes Article 6 PCT.

7. The passage "characterized in that it is capable of inhibiting any site in the Factor VIII molecule which is susceptible to being lysed by an anti-Factor VIII allo-antibody" is defined as results to be achieved and therefore lacks clarity (Article 6 PCT). It appears possible to define the subject matter in more concrete terms, viz. in terms how the effect, i.e. inhibiting any site in the Factor VIII molecule which is susceptible to being lysed, is to be achieved (see e.g. the technical features of claims 13-15).

8. The subject matter of claim 17 does not meet the requirements of Article 6 PCT in that the subject matter for which protection is sought is not defined. Said claim attempts to define the subject-matter in terms of the result to be achieved and is not allowable, because it appears possible to define the subject matter in more concrete terms, viz. in terms of how the effect, i.e. the inhibition of the activity of a Factor VIII allo-antibody, is to be achieved (see e.g. the technical features in claims 18 and 19).

9. Claims 24 and 27 suffer from a lack of clarity (Article 6 PCT), because they are formulated as second medical indication claims, but are not defined by a medical indication. The passage "treatment of a mammal.... in the blood thereof" in claims 24 and 27 defines no medical indication (i.e. disease).

10. The use of "in particular" renders the passage "in particular for the treatment of a mammal suffering...." in claim 27 non-limiting for the scope of said claim and introduces ambiguity in the protection sought and therefore contravenes Article 6 PCT.

PATENT COOPERATION TREATY

# PCT

14 NOV 2001

PCT

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| H153030-4WO | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/EP00/06870 | 18/07/2000 | 21/07/1999 |
| International Patent Classification (IPC) or national classification and IPC | | |
| G01N33/68 | | |
| Applicant | | |
| INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE M | | |

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1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 31/01/2001 | 12.11.2001 |
| Name and mailing address of the international preliminary examining authority: | Authorized officer |
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Weijland, A<br>Telephone No. +49 89 2399 7400 |

the subject matter of claims 17-19, **since a hitherto unknown property,** i.e. inhibiton of Factor VIII cleavage by allo-antibodies, **cannot render a known product,** i.e. AEBSF, **novel** (the Guidelines C-III 4.8).

2. Inventive Step (Article 33(3) PCT)

2.1 The subject matter of claims 1-12 would appear to involve an inventive step.

D1 is considered to be the closest prior art. D1 (abstract; page 7729, left column, 8 paragraph) describes the localization of human factor VIII inhibitor epitopes for 22 allo-antibodies by immunoblotting. Claim 1 differs from D1 in that it relates to a method of defermining the presence of anti-Factor VIII allo-antibodies by determining the **degradation** of Factor VIII.

The skilled person, equipped with knowledge of D1, would never be motivated to arrive at the subject matter of claim 1, since it has not been suggested in D1 alone or in combination with any other prior art document that said allo-antibodies **degrade** Factor VIII. The same applies to claims 2-12.

2.2 The subject matter of claims 13-16, 20-22 would appear to involve an inventive step.

Claim 13-16 and 20-22, relating to specific peptides sequences that are novel (see section 2.1), would appear to involve an inventive step, since it has not been suggested in the prior art documents that these sequences as part of peptides (claims 13-16) or inhibitors (claims 20-22) are capable of inhibiting the **degradation** of Factor VIII.

2.3 The subject matter of claims 23-27 would appear to involve an inventive step.

D1 (abstract; page 7732, right column) suggests the use of peptides derived from epitopes on Factor VIII and recognized by allo-antibodies as therapeutic agents to block inhibition of Factor VIII activity.

Claims 23 and 24 differ from D1 in that they relate to a pharmaceutical

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-16,20-27 |
| | No: | Claims | 17-19 |
| Inventive step (IS) | Yes: | Claims | 1-16, 20-27 |
| | No: | Claims | 17-19 |
| Industrial applicability (IA) | Yes: | Claims | 1-27 |
| | No: | Claims | |

2. Citations and explanations
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
**see separate sheet**

composition comprising an anti-Factor VIII allo-antibody (claim 23) or the use thereof in the preparation of a pharmaceutical composition.

Claims 23 and 24 would appear to involve an inventive step, since the presence of degrading anti-Factor VIII allo-antibodies as part of a pharmaceutical composition or the use thereof has not been suggested before in the art and implicates a functional role of said antibodies by inhibiting pro-coagulant activity faster than non-catalysing anti-Factor VIII antibodies (page 13, lines 13-15 of the description). For the same reasons mentioned above, also claim 25 involves an inventive step.

Claims 26 and 27, relating to a pharmaceutical composition containing a Factor VIII degradation inhibitor or the use thereof in the preparation of a composition would appear to involve an inventive step, since the degradation of Factor VIII by an allo antibody has not been suggested in the art and consequently neither the use of its inhibitors.

**SECTION VII**

3. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 is not mentioned in the description, nor is this document identified therein.

**SECTION VIII**

4. The use of "preferably" renders the passage "preferably activated with cyanogen bromide" in claim 4 non-limiting for the scope of said claim and introduces ambiguity in the protection sought and therefore contravenes Article 6 PCT.

5. In order to meet the requirements of clarity the term "sequence" in claims 13-15 needs to be replaced by "peptide sequence" Article 6 PCT.

6. The term "peptide or non-peptide analogue" in present claim 16 introduces ambiguity in the scope for which protection is sought and therefore contravenes Article 6 PCT.

The following documents (D) are referred to in this report:

D1: C. A. FULCHER ET AL.: 'Localization of human factor FVIII inhibitor epitopes to two polypeptide fragments.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 82, November 1985 (1985-11), pages 7728-7732, XP002125713 NATIONAL ACADEMY OF SCIENCE. WASHINGTON., US ISSN: 0027-8424

**SECTION V**

1. Novelty (Article 33(2) PCT)

1.1 The subject matter of claims 1-16 and 20-27 is novel.

Claim 1, relating to determining the presence of anti-Factor VIII allo-antibodies capable of **degrading** Factor VIII comprising the detection of degradation of Factor VIII by anti-Factor VIII allo antibodies, is not disclosed in the prior art documents.

Claims 13-16 and 20-22, relating to sequences (claims 13-15), peptides (claim 16) or inhibitors (claims 20-22) having defined sequences according to claims 13-15 are not disclosed in the prior art documents.

Claims 23-27, relating to pharmaceutical compositions including anti-Factor VIII allo-antibodies or its inhibitors (claims 23 and 26 respectively) and uses of anti-Factor VIII allo-antibodies for the preparation of a pharmaceutical composition (claims 24, 25) and inhibitors thereof (claim 27), are not disclosed in the prior art documents.

1.2 The subject matter of claims 17 to 19 is not novel.

Claim 17 is related to a degradation inhibitor. Compounds that encompass the scope of this claim are mentioned on page 6 (lines 20 to 30) of the description, such as PMSF or AEBSF that are commercially available and inhibit the cleavage of Factor VIII at certain positions. The existence of these molecules anticipates

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06870

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

1-21 as originally filed

**Claims, No.:**

1-27 as originally filed

**Drawings, sheets:**

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.: